UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAY W. WOOD, LAN DeCASTRO, and H. WILLIAM BOSCH

Appeal 2007-2212
Application 10/667,472
Technology Center 1600

Decided: September 20, 2007

Before DEMETRA J. MILLS, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 10-22 and 24-26.[1] We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Claims 23 and 27-74 are also pending, but stand withdrawn from consideration (Br. 3).

Representative claim follows.

10. A nanoparticulate composition comprising:
(a) beclomethasone dipropionate particles having an average particle size of less than about 1000 nm; and
(b) at least one surface modifier.

Cited References:

Liversidge US 5,145,684 Sep. 8, 1992

Lacy et al., *Drug Information Handbook* (*LEXI- Comp, Inc.*), pp. 95-96 (1993). (Drug)

Grounds of Rejection

Claims 10-22 and 24-26 stand rejected under 35 U.S.C. § 103(a) as obvious over Liversidge in view of Drug. We select claim 10 as representative of the claims before us as Appellant has not separately argued individual claims of the rejection. 37 C.F.R. 41.37(c)(1)(vii) (2006).

DISCUSSION

Background

Delivery of therapeutic agents to the respiratory tract is important for both local and systemic treatment of disease. (Specification 1.) With conventional techniques, delivery of agents to the lung is extremely inefficient. (*Id.*) Attempts to develop respirable aqueous suspensions of poorly soluble compounds have been unsuccessful. (*Id.*) Micronized therapeutic agents suspended in aqueous media are too large to be delivered by aerosolized aqueous droplets. (*Id.*) With conventional processes, it is estimated that only about 10 to 20% of the agent reaches the lung. (*Id.*)

The efficiency of respiratory drug delivery is largely determined by the particle size distribution. (*Id.*) Large particles (greater than 10 m) are primarily deposited on the back of the throat. (*Id.*) Greater than 60% of the particles with sizes between 1 and 10 m pass with the air stream into the upper bronchial region of the lung where most are deposited. (*Id.*) With particles less than about 1 μm, essentially all of the particles enter the lungs and pass into the peripheral alveolar region; however, about 70% are exhaled and therefore are lost. (*Id.*)

Appellants claim a nanoparticulate composition comprising: beclomethasone dipropionate particles having an average particle size of less than about 1000 nm; and at least one surface modifier.

Obviousness

Claims 10-22 and 24-26 stand rejected under 35 U.S.C. § 103(a) as obvious over Liversidge in view of Drug Information Handbook (Drug).

The Examiner finds

> Liversidge et al teach dispersible particles consisting essentially of a crystalline drug substance having a *surface modifier* adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of *less than about 400 nm* (see abstract and col. 1, lines 32-43). . . . Suitable drugs include *corticosteroids, such as steroid A*. The surface modifiers can be selected from the group including non-ionic and anionic surfactants such as polyvinylpyrrolidone (see cols. 3-4).
>
> Liversidge also discloses that the effective average particle size of less than 400 nm, or *less than 100 nm* is preferred. Also at least 99% of the particles have a particle size less than the effective average, eg. 400 nm (see col. 5, lines 26-40).

> Liversidge teaches that the surface modifier can be present in an amount of 0.1 to 90%, preferably 20-60% by weight based on the total weight of dry particles (col. 7, lines 15-20). Liversidge, while disclosing corticosteroids, such as *steroid A* as suitable active agents for nanoparticulate formulations, lacks specific disclosure of beclomethasone dipropionate.

(Answer 3.)

The Examiner relies on Drug for the disclosure of beclometha-sone dipropionate (a corticosteroid) as a suitable active agent for formulations for delivery into lungs or nasal passages. (Answer 4.)

The Examiner concludes

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made, given the general formulations of Liversidge on formulations containing active agents including corticosteroids, to have looked in the art for other specific species of corticosteroids suitable for formation of compositions, as disclosed in Drug Information Handbook, with reasonable expectations of successfully preparing formulations comprising different active agents for treating different disorders.

(Answer 4.)

In order to determine whether a prima facie case of obviousness has been established, we considered the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996); (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

Liversidge teaches nanoparticles that are treated with a surface modifier, that such nanoparticles provide for greater bioavailability of the drug, and that many different types of drugs, including steroids, may be delivered in the form of nanoparticles. (Answer 3.) The difference between the claimed invention and Liversidge, is that Liversidge does not teach the particular beclamethasone diproprionate drug, instead teaching nanoparticles of steroids and corticosteroids, generally. (Answer 3.) Drug teaches it is known to deliver the corticosteroid, beclamethasone dipropionate, to the lungs or nasal passages for the treatment of asthma. Thus, when combined, all the claim limitations are disclosed in the prior art. We find the Examiner has provided sufficient evidence and an indicated a sufficient reason for one of ordinary skill in the art to use Drug's known steroid, beclamethasone diproprionate, in the form of a surface modified nanoparticle to support a prima facie case of obviousness. (Answer 4.)

Appellants contend that the Examiner failed to establish a prima facie case of obviousness because there is no motivation to combine Liversidge with Drug. (Br. 4.) Appellants argue, since "Liversidge listed corticosteroids as a class of drugs from which 'suitable drug substances can be selected,'" there is no motivation to select beclamethasone from among the many known corticosteroids in the prior art. (Br. 6-7.) Appellants argue that simply selecting a beclomethasone as known corticosteroid is a proscribed obvious to try rationale. (Reply Br. 5.)

We find the Examiner's indicated motivation to combine Liversidge and Drug is sufficient to support a prima facie case of obviousness. Liversidge discloses that the surface modified nanoparticles of drug may be used to orally administer a wide variety of drug substances, including steroids and

corticosteroids. (Liversidge, col. 3, ll. 38-40; col. 3, l. 53 to col. 4. l. 14.) Liversidge further describes a screening method to discern which types of drugs may be administered with the most compatible surface modifiers. (Liversidge, col. 7, ll. 21-46.) One of ordinary skill in the art, understanding that the surface modified nanoparticles of Liversidge provide for greater bioavailability of drug, and knowing that drug delivery to the lung is difficult, would have been motivated to deliver a corticosteroid intended for delivery to the lung to treat asthma, such as beclamethosone diproprionate in the form of the surface modified nanoparticles for the purpose of increasing bioavailability of the drug to the lungs. The Examiner additionally argues that the claims are broad and are not limited to surface modifiers that provide a stable composition of beclomethasone dipropionate, indicating there are no exclusions in the claims of surface modifiers which would not provide for a stable drug. (Answer 6.)

Furthermore, it is error to conclude that

> a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.' . . . When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103."

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007). Therefore, we are not persuaded by Appellants arguments against a prima facie case of obviousness.

Appellants further argue that if a prima facie case of obviousness has been established, it has been rebutted with evidence of unexpected results. (Br. 4.) In particular, Appellants argue that

> Example 1 of the specification describes the preparation of a nanoparticulate beclomethasone composition . . . and compares it to a conventional beclomethasone composition. The specification states that "only about 7% of the [beclomethasone] presented as a suspension or raw drug substance reaches the impactor." On the other hand, "the use of nanoparticles led to a significantly higher fraction reaching the impactor." In addition, a greater fraction of beclomethasone remained in the nebulizer when raw drug substance rather than the nanoparticulate form was used. Thus, the experimental results demonstrate that the nanoparticulate form of beclomethasone results in less waste and more effective delivery. (*Id.* at 9.)

We are not persuaded by Appellants' presentation of alleged unexpected results. Liversidge discloses that "extremely small effective average particle size can be prepared by wet milling in the presence of grinding media in conjunction with a surface modifier, and that such particles are stable and do not appreciably flocculate or agglomerate due to interparticle attractive forces". (Liversidge, col. 3, ll. 15-31). These particles "can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability." (Liversidge, col. 3, ll. 15-31). Liversidge further teaches surface modified nanoparticles of corticosteroids. (Liversidge, col. 11, l. 40 to col. 12, l. 25.)

We do not find that Appellants have compared the nanoparticles of the claimed invention with the closest prior art, Steroid A of Liversidge. When relying on comparative testing, the applicant is under a duty to compare his claimed invention with the closest prior art (i.e., steroid A of

Liversridge). *See, e.g., In re Burckel*, 592 F.2d 1175, 1179, 201 USPQ 67, 71 (CCPA 1979); *In re Merchant*, 575 F.2d 865, 869, 197 USPQ 785, 788 (CCPA 1978) ("An applicant relying upon a comparative showing to rebut a prima facie case must compare his claimed invention with the closest prior art").

Appellants have failed to explain how the data in Example 1 show unexpected results over the closest prior art, i.e., Liversidge. In addition, Appellants' data are not commensurate in scope with claim 10. First, the beclomethasone diproprionate particle size distribution in Example 1 is 0.26 ± 0.13 *mm* ($0.26x10^6\pm0.13x10^6$ nm) (Spec. 20), with 80% of the particles being "less than 2.5 mm" (less than $2.5x10^6$ nm) (Spec. 22). These values are much greater than those of claim 10 which requires "an average particle size of less than about 1000 nm." Second, only Formulation IV in Table II appears to show superior results to Formulation I (the comparative example), suggesting that only a surfactant concentration of 0.1% dispersed in a 6 mL volume provides for substantially greater bioavailability of beclamethasone diproprionate. (Spec. 23.) Again, claim 10 is not so limited. Thus, these data are not sufficient to overcome the Examiner's prima facie case of obviousness.

Moreover "when the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740, 82 USPQ2d 1385, 1396 (2007). In the present case, the prior art evidences that when nanoparticles are treated with a surface modifier adsorbed on the

surface, such particles are stable and have a high bioavailability. Thus the function of the surface modifier of Liversidge is to yield higher bioavailability of the nanoparticle. (Liveridge, col. 3, ll. 1-23.) One of ordinary skill in the art would thus also expect Appellants' nanoparticles treated with a surface modifier to provide for a higher bioavailability. Such expected beneficial results are evidence of obviousness just as unexpected beneficial results are evidence of unobviousness. *See In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 82 (CCPA 1975). In the present case, one of ordinary skill in the art would have expected surface-modified nanoparticles to provide greater bioavailability of beclamethasone diproprionate in view of the disclosures of Liversidge and Drug.

The obviousness rejection is affirmed.

CONCLUSION

The obviousness rejections are affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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